

REMARKS

Reconsideration and allowance are respectfully requested.

The specification has been amended to delete reference to hyperlinks. The sequence of IGFBP-4, in its mature (SEQ ID NO:2) and pro-form (SEQ ID NO:1) has been incorporated in the specification by submission of a Sequence Listing herewith. The material inserted is the material previously incorporated by reference, corresponding to the SwissProt Accession number disclosed in the specification (P22692) (SEQ ID NO:1) and the mature form (SEQ ID NO:2). No new matter is added by the amendment to enter the Sequence Listing. Applicants have attached, at Tab A, the SwissProt entry for P22692, showing that the sequence reported was changed once, on March 1, 1992, and remained static thereafter. Thus, the sequence in SwissProt with accession number P22692 was the same on the priority date of the present application as it is today and as submitted in the Sequence Listing. The amendments to the claims are made to replace the references to insulin-like growth factor binding protein 4 with reference to SEQ ID NO:2, and to clarify some claim language. No new matter has been added by the present amendments to the claims or specification.

The Rejections Under 35 U.S.C. § 112, second paragraph

Claims 10 to 16 were rejected as indefinite, based on the recitation of insulin-like growth factor binding protein 4 in the claims. The Examiner states that this recitation does not particularly identify the protein. Applicants respectfully submit that the amendments to the claims, which now recite "SEQ ID NO:2", instead of "insulin-like growth factor binding protein 4" obviate any indefiniteness as to the identity of the protein component of the conjugate being claimed. This amendment also defines the conjugation points recited in the dependent claims. Claim 15 has been amended to make clear that it is a product by process claim. All claims formerly dependent on claim 1 have now been made dependent on pending claim 10. Accordingly, it is respectfully requested that the rejections under 35 U.S.C. 112, second paragraph, be withdrawn.

The Rejections Under 35 U.S.C. § 112, first paragraph

Claims 10 to 16 were rejected for lack of written description. It is respectfully submitted that the amendment of the claims to recite "SEQ ID NO:2" instead of "insulin-like growth factor binding protein-4" obviates the grounds for this rejection, as it is respectfully submitted that the identity of the claimed conjugates is clearly delineated and would be apparent to one of ordinary skill in the art.

Claims 10 to 16 were also rejected for lack of enablement. The ground stated by the Examiner appears to be one of scope, based on the interpretation that insulin-like growth factor binding protein 4 encompasses a large genus of proteins. The amendment to the claims replacing recitations of "insulin-like growth factor binding protein 4" with "SEQ ID NO:2" is respectfully submitted to overcome this ground for rejection.

In light of the amendments to the claims and the comments above, it is respectfully requested that the rejection of claims 10 to 16 under 35 U.S.C. 112, first paragraph should be withdrawn.

The Rejections Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 10 and 14 to 16 as obvious over the disclosure of WO1994/22466 ("Cox") in view of Bethel. Applicants traverse, and request reconsideration.

The Examiner cites Cox for its disclosure of pegylated IGFBP-1, and Bethel for the sequence of IGFBP-4. The Examiner also apparently attributes to Cox the teaching that "...PEGylation of IGFBPs was know to increase the serum half-life of the polypeptides, while retaining their activity..." This last statement is unsupported by Cox. At page 12, lines 6 to 20, of Cox, it is disclosed that in order to link PEG to IGFBP-1, one should create a mutant molecule that contains cysteines in non-wild type positions, in order to reduce the possibility that the PEG molecules will bind to cysteines that are involved in receptor binding or IGF binding. Thus, Cox teaches that in order to maintain activity with a pegylated IGFBP-1, you need to mutate it, i.e., that an unmutated IGFBP pegylated at a native cysteine will lose activity, be it receptor binding or IFG binding.

Thus, from the teaching of Cox and Bethel, alone or in combination, it cannot be concluded that a pegylation of SEQ ID NO:2, as presently claimed, would result in a biologically active molecule, and one of ordinary skill in the art would have actually concluded, based on the disclosure of Cox, that one would have needed to modify the sequence of SEQ ID NO:2 to add non-wild type cysteines in order to get a pegylated, active molecule.

Further, even if the cited prior art provided any basis for concluding that there was a reasonable expectation that one could pegylate one or more wild-type cysteines of SEQ ID NO:2 and retain activity, there are 20 cysteines in SEQ ID NO:2 that could potentially be modified, and the cited art clearly is devoid of any guidance as to which of these could be modified without losing activity. There is also no hint in any of the cited that the modification of SEQ ID NO:2 at cysteines 110 and/or 117 would provide a pegylated protein with the improved properties recited in the present specification, e.g., see page 4, lines 3 to 10.

Because claims 10 and 14 to 16 cannot properly be said to be obvious over the combined disclosures of Cox and Bethel, claims 11 to 13, dependent on claim 10, cannot be said to be obvious over the combined disclosures of Cox, Bethel, and Veronse.

The Examiner has rejected claims 10 and 14 to 16 over the disclosures of U.S. Patent 6,004,775 ("Shimasaki") in view of U.S. Patent 6,207,640 ("Attie") and Francis et al. ("Francis"). Applicants traverse, and request reconsideration.

Shimasaki is cited for the disclosure of the amino acid sequence of IGFBP-4, and that such peptides are useful as components of antineoplastic compositions. The Examiner acknowledges that Shimasaki is silent with respect to pegylation of IGFBP-4. Attie is cited for the disclosure of pegylation of IGF-I or growth hormone to improve the circulating half life of these proteins. Francis is cited for a general disclosure about the advantages that can be provided by pegylation of therapeutic proteins. The Examiner asserts that the combined teachings of these references would have provided reasons

to one of ordinary skill in the art to make the presently claimed conjugates, with a reasonable expectation of success.

Applicants point to Cox, above, and the Examiner's comments with respect to enablement for proof that one of ordinary skill in the art would have had no reasonable expectation of success that modifying any of the cysteines of SEQ ID NO:2 would have yielded an active conjugate. As noted above, Cox teaches that one needs to provide non-native cysteines if one wants to conjugate IGFBP-1 with polyethylene glycol and retain activity. The Examiner provides a discourse on the unpredictability that modifications to protein structures can have on activity. Clearly, then, one of ordinary skill in the art would have no idea what effect modification of any of the 20 particular cysteines of SEQ ID NO:2 would have on the activity, and based on Cox would avoid such modifications and only modify on non-native, mutant cysteines. None of Shimasaki, Attie, or Francis provides any guidance as to which, if any, of the native cysteines of SEQ ID NO:2 can be pegylated while retaining activity, much less why one would choose the specific cysteines 110 and 117 recited in the present claims. Thus, it is respectfully submitted that the cited combination of prior art (Shimasaki, Attie, Francis) cannot properly be said to render the present claims obvious.

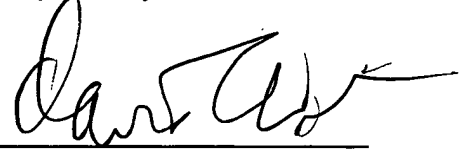
Because the combination of Shimasaki, Attie, and Francis do not render claim 10 obvious, the combination of Shimasaki, Attie, Francis, and Veronse cannot render dependent claims 11 to 13 obvious.

In light of the above remarks and amendments, it is respectfully submitted that all grounds for the rejection of claims 10 to 16 as obvious have been overcome, and the rejection should be withdrawn.

Appl. No. 10/529,090
Filed: September 30, 2005

No further fee is required in connection the filing of this Amendment. If any additional fees are deemed necessary, authorization is given to charge the amount of any such fee to Deposit Account No. 08-2525.

Respectfully submitted,



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316813

UniProtKB/Swiss-Prot entry P22692

Entry information

Entry name	IBP4_HUMAN
Primary accession number	P22692
Secondary accession numbers	None
Integrated into Swiss-Prot on	August 1, 1991
Sequence was last modified on	March 1, 1992 (Sequence version 2)
Annotations were last modified on	November 13, 2007 (Entry version 87)

Name and origin of the protein

Protein name	Insulin-like growth factor-binding protein 4 [Precursor]
Synonyms	IGFBP-4 IBP-4 IGF-binding protein 4
Gene name	Name: IGFBP4 Synonyms: IBP4
From	Homo sapiens (Human) [TaxID: 9606]
Taxonomy	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo.
Protein existence	1: Evidence at protein level;

References

- [1] NUCLEOTIDE SEQUENCE [MRNA].
PubMed=1707125
Latour D., Mohan S., Linkhart T.A., Baylink D.J., Strong D.D.;
"Inhibitory insulin-like growth factor-binding protein: cloning, complete sequence, and physiological regulation.";
Mol. Endocrinol. 4:1806-1814(1990).
- [2] NUCLEOTIDE SEQUENCE [MRNA].
TISSUE=Placenta;
PubMed=1704481
Shimasaki S., Uchiyama F., Shimonaka M., Ling N.;
"Molecular cloning of the cDNAs encoding a novel insulin-like growth factor-binding protein from rat and human.";
Mol. Endocrinol. 4:1451-1458(1990).
- [3] NUCLEOTIDE SEQUENCE [MRNA], AND PROTEIN SEQUENCE OF 22-41.
TISSUE=Osteosarcoma;
PubMed=1709161
Kiefer M.C., Masiarz F.R., Bauer D.M., Zapf J.;
"Identification and molecular cloning of two new 30-kDa insulin-like growth factor binding proteins isolated from adult human serum.";
J. Biol. Chem. 266:9043-9049(1991).

[4] NUCLEOTIDE SEQUENCE [GENOMIC DNA].**TISSUE**=Placenta;

Strong D.D., Morales S., Lee K., Boonyaratanakornkit V., Baylink D.J., Mohan S.;

"Cloning of the human insulin-like growth factor binding protein-4 gene and identification of the proximal promoter.";

Submitted (FEB-1995) to the EMBL/GenBank/DDBJ databases.

[5] NUCLEOTIDE SEQUENCE [LARGE SCALE MRNA].

Kalnine N., Chen X., Rolfs A., Halleck A., Hines L., Eisenstein S., Koundinya M., Raphael J., Moreira D., Kelley T., LaBaer J., Lin Y., Phelan M., Farmer A.;

"Cloning of human full-length CDSs in BD Creator(TM) system donor vector.";

Submitted (MAY-2003) to the EMBL/GenBank/DDBJ databases.

[6] NUCLEOTIDE SEQUENCE [GENOMIC DNA].

Rieder M.J., Livingston R.J., Daniels M.R., Chung M.-W., Miyamoto K.E., Nguyen C.P., Nguyen D.A., Poel C.L., Robertson P.D., Schackwitz W.S., Sherwood J.K., Witrak L.A., Nickerson D.A.;

"NIEHS-SNPs, environmental genome project, NIEHS ES15478, Department of Genome Sciences, Seattle, WA (URL: <http://egp.gs.washington.edu>).";

Submitted (OCT-2003) to the EMBL/GenBank/DDBJ databases.

[7] NUCLEOTIDE SEQUENCE [LARGE SCALE MRNA].**TISSUE**=Colon;

DOI=10.1101/gr.2596504; PubMed=15489334

The MGC Project Team;

"The status, quality, and expansion of the NIH full-length cDNA project: the Mammalian Gene Collection (MGC).";

Genome Res. 14:2121-2127(2004).

[8] PROTEIN SEQUENCE OF 22-53.**TISSUE**=Colon;

PubMed=1709585

Culouscou J.-M., Shoyab M.;

"Purification of a colon cancer cell growth inhibitor and its identification as an insulin-like growth factor binding protein.";

Cancer Res. 51:2813-2819(1991).

Comments

- **FUNCTION:** IGF-binding proteins prolong the half-life of the IGFs and have been shown to either inhibit or stimulate the growth promoting effects of the IGFs on cell culture. They alter the interaction of IGFs with their cell surface receptors.
- **SUBUNIT:** Binds IGF2 more than IGF1.
- **SUBCELLULAR LOCATION:** Secreted.
- **SIMILARITY:** Contains 1 IGFBP N-terminal domain.
- **SIMILARITY:** Contains 1 thyroglobulin type-1 domain.

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Sequence databases	
	M38177; -; NOT_ANNOTATED_CDS; mRNA.

EMBL	M62403; AAB06189.1; -; mRNA. U20982; AAA62670.1; -; Genomic_DNA. BT019892; AAV38695.1; -; mRNA. AY442346; AAR05443.1; -; Genomic_DNA. BC016041; AAH16041.1; -; mRNA.
PIR	G01662; B37252.
RefSeq	NP_001543.2; -.
UniGene	Hs.462998
3D structure databases	
PDB	1WQJ; X-ray; 1.60 A; B=24-103. 2DSP; X-ray; 2.50 A; B=22-113. 2DSQ; X-ray; 2.80 A; A/B=22-113. 2DSR; X-ray; 2.10 A; B=24-103, G=172-253.
SMR	P22692; 23-113, 172-250.
Polymorphism databases	
NIEHS-SNPs	IGFBP4.
Organism-specific databases	
H-InvDB	HIX0013798; -.
HGNC	HGNC:5473; IGFBP4.
GeneLynx	IGFBP4; Homo sapiens.
GenAtlas	IGFBP4.
MIM	146733; gene.
PharmGKB	PA29706; -.
Gene expression databases	
ArrayExpress	P22692; -.
CleanEx	HS_IGFBP4; -.
GermOnline	ENSG00000141753; Homo sapiens.
Ontologies	
GO	GO:0008283; Biological process: cell proliferation (<i>traceable author statement from ProtInc</i>). GO:0006259; Biological process: DNA metabolic process (<i>traceable author statement from ProtInc</i>). GO:0007165; Biological process: signal transduction (<i>traceable author statement from ProtInc</i>). GO:0001501; Biological process: skeletal development (<i>traceable author statement from ProtInc</i>).
Family and domain databases	
InterPro	IPR012212; IGFBP-4. IPR009168; IGFBP1-6. IPR000867; IGFBP_like. IPR000716; Thyroglobulin_1.
PANTHER	PTHR11551; IGFBP1-6; 1.
Pfam	PF00219; IGFBP; 1. PF00086; Thyroglobulin_1; 1.

PIRSF	PIRSF500004; IGFBP-4; 1. PIRSF001969; IGFBP1-6; 1.
SMART	SM00121; IB; 1. SM00211; TY; 1.
PROSITE	PS00222; IGFBP_N_1; 1. PS51323; IGFBP_N_2; 1. PS00484; THYROGLOBULIN_1_1; 1. PS51162; THYROGLOBULIN_1_2; 1. PROSITE graphical view of domain structure (profiles).
Proteomic databases	
PeptideAtlas	P22692; -.
Genome annotation databases	
Ensembl	ENSG00000141753; Homo sapiens.
GeneID	3487; -.
KEGG	hsa:3487; -.
Other	
Implicit links to	GeneCards; SOURCE; ProDom; BLOCKS; ProtoNet; ModBase; UniRef.

Keywords

3D-structure; Direct protein sequencing; Glycoprotein; Growth factor binding; Polymorphism; Secreted; Signal.

Features

Key	From	To	Length	Description	FTId
SIGNAL	1	21	21		
CHAIN	22	258	237	Insulin-like growth factor-binding protein 4.	PRO_000001438
DOMAIN	23	103	81	IGFBP N-terminal.	
DOMAIN	171	249	79	Thyroglobulin type-1.	
CARBOHYD	125	125		N-linked (GlcNAc...) (Potential).	
DISULFID	38	59		By similarity.	
DISULFID	44	56		By similarity.	
DISULFID	67	80		By similarity.	
DISULFID	74	100		By similarity.	
DISULFID	131	138		By similarity.	
DISULFID	174	204		By similarity.	
DISULFID	215	226		By similarity.	
DISULFID	228	249		By similarity.	
VARIANT	42	42	1	V -> G (in dbSNP:rs599199 [NCBI]).	VAR_011906
CONFLICT	51	51		P -> A (in Ref. 1, 4 and 8).	
CONFLICT	198	198		I -> F (in Ref. 1 and 4).	
HELIX	32	36	5		
STRAND	45	49	5		
STRAND	56	59	4		
STRAND	78	81	4		
HELIX	89	94	6		

STRAND	98	102	5
HELIX	173	186	14
HELIX	195	198	4
STRAND	208	210	3
STRAND	212	215	4
STRAND	226	229	4
TURN	231	233	3
HELIX	244	246	3

Sequence information

Length: **258 AA** [This is the length of the unprocessed precursor]

Molecular weight: **27934 Da** [This is the MW of the unprocessed precursor]

CRC64: **5E8F4638D99F0A94** [This is a checksum on the sequence]

<u>10</u>	<u>20</u>	<u>30</u>	<u>40</u>	<u>50</u>	<u>60</u>
MLPLCLVAAL	LLAAGPGPSL	GDEAIHCPPC	SEEKLARCRP	PVGCEELVRE	PGCGCCATCA
<u>70</u>	<u>80</u>	<u>90</u>	<u>100</u>	<u>110</u>	<u>120</u>
LGLGMPCGVY	TPRCGSGLR	CYPPRGVEKPL	HTLMHGQGV	CMLAEIEAIQ	ESLQPSDKDE
<u>130</u>	<u>140</u>	<u>150</u>	<u>160</u>	<u>170</u>	<u>180</u>
GDHPNNSFSP	CSAHDRRLQ	KHFAKIRDRS	TSGGKMKVNG	APREDARPVP	QGSCQSELHR
<u>190</u>	<u>200</u>	<u>210</u>	<u>220</u>	<u>230</u>	<u>240</u>
ALERLAASQS	RTHEDLYIIP	IPNCDRNGNF	HPKQCHPALD	GQRGKCWCVD	RKTGVKLPGG
<u>250</u>					
LEPKGELDCH	QLADSFRE				

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Primary accession number or entry name:

Date: day-month-year (e.g. 30-11-1998 or 30-NOV-1998) or year-month-day.

87 matches

 UniProtKB

	Status	Primary Accession	Entry Name	Entry Version	Sequence Version	Release	Date		
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